IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Van Beusechem	Examiner: Scott Long
Serial No: 10/501,407	Group Art Unit: 1633
Confirmation No.: 9615	Docket No.: 294-293 PCT/US/RCE
Filing Date: March 25, 2005	Dated: April 4, 2011

For: VIRUSES WITH ENHANCED LYTIC POTENCY

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(Printed Name)

Signature: /Lauren T. Emr/

RESPONSE TO OFFICE ACTION

Sir:

In response to an office action mailed December 2, 2010, Applicants respectfully submit the following declaration under 37 C.F.R. 1.132 and remarks. The response is being filed within the fourth month from the mailing date of the office action. Therefore, a petition for a one-month extension of time is being filed herewith. Reconsideration is respectfully requested.

A listing of the claims begins on page 2 of this paper.

Remarks begin on page 8 of this paper

The following is a listing of the pending claims:

1-9. Cancelled

10. (Withdrawn) The recombinant virus according to claim 1, wherein the restoring factor is chosen from the group consisting of p53, p63, p73, BAX, BAK, BOK/Mtd, BCL-Xs, Noxa/APR, PIDD, p53AIP1, PUMA,KILLER/DR5, Apaf-1, PIG, BID, tBID, BAD, HRK, Bik/Nbk, BLK, mda-7, p14ARF or functional variants, analogues or derivatives thereof.

11-14. Cancelled

15. (Withdrawn) Use of the recombinant virus according to claim 1 in a medicament.

16. (Withdrawn) Use according to claim 15 for the manufacture of a medicament for suppressing uncontrolled cell growth.

17. (Withdrawn) A method for lysing target cells hampered in the p53 dependent apoptosis pathway, comprising the steps of:

-infecting the said target cells with the replication competent recombinant virus according to claim 1, and

-replicating said virus within said target cells, further comprising the step of providing, in the virus genome, the coding sequence of at least one restoring factor functional in restoring the p53 dependent apoptosis pathway, said coding sequence being capable to be expressed in the target cells upon infection thereof by said virus.

18. Cancelled

19. (Withdrawn) The method according to claim 17, further comprising the step of subjecting said target cells to at least one of irradiation and a toxic chemical compound.

20. (Withdrawn) The method according to claim 17, wherein said target cells are present in an animal body.

21. (Withdrawn) A method for treatment of a subject body suffering from a condition involving body cells hampered in a p53 dependent apoptosis pathway, comprising the step of administering to said subject body an effective amount of the replication competent recombinant adenovirus according to claim 1.

22. (Withdrawn) The method according to claim 21, wherein the condition is associated with uncontrolled cell growth.

23. (Withdrawn) The method according to claim 22, wherein the condition is chosen from the group consisting of cancer, arthritis, and vascular smooth muscle cell hyperplasia.

24-25. Cancelled.

26. (Previously presented) A replication competent recombinant adenovirus, being capable to replicate and having lytic capacity in target cells, wherein said target cells are hampered in a p53 dependent apoptosis pathway, wherein the adenovirus is a conditionally replicating adenovirus; wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells; wherein said coding sequence is operably linked to one or more expression control sequences functional in said target cells, whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to the recombinant adenovirus lacking said coding sequence, and wherein the virus genome further comprises a gene selected from a gene encoding the adenovirus E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof.

27. (Previously presented) The recombinant virus according to claim 26, wherein the virus is a human adenovirus.

28. (Previously presented) The recombinant virus according to claim 26, wherein expression of at least one essential early adenovirus gene is controlled by a tumor-specific promoter.

29. (Previously presented) The recombinant virus according to claim 26, wherein the adenovirus is a heterologously trans-complemented adenovirus.

30. Cancelled

31. Cancelled

32. (Previously presented) The recombinant virus according to claim 26, wherein the virus genome comprises one or more of the genes of the adenovirus E4 region encoding E4 proteins or functional analogues or derivatives thereof.

33. (Previously presented) The recombinant virus according to claim 26, wherein the virus genome comprises a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E4 or F6 protein or functional analogues or derivatives thereof.

34. (Previously presented) The recombinant virus according to claim 26, wherein the adenovirus carries a mutation in a E1A region encompassing at least part of the pRb-binding CR2 domain of E1A.

35. (Previously presented) The recombinant virus according to claim 26, wherein the restoring factor is p53 protein or a functional analogue or derivative thereof.

36. (Previously presented) The recombinant virus according to claim 35, wherein the protein lacks a functional binding domain for a human MdM2 protein.

37. (Previously presented) The recombinant virus according to claim 35, wherein the protein is a functional derivative of human p53 with mutated amino acids Leu-14 and Phe-19.

38. (Previously presented) The recombinant virus according to claim 26, wherein the target cell is a human cell chosen from the group consisting of cancer cells, arthritic cells, hyperproliferative vascular smooth muscle cells and cells infected with a virus other than said recombinant virus.

39. (Previously presented) The recombinant virus according to claim 27, wherein the human adenovirus comprises serotype 5.

40. (Previously presented) The recombinant virus according to claim 34, wherein the mutation comprises a deletion encompassing amino acids 122-129 (LTCHEAGF) of SEQ ID NO: 5.

41. Cancelled.

REMARKS

In an office action, claims 26-29 and 32-40 have been rejected. In response, Applicants provide the herein declaration under 37 C.F.R. 1.132 and remarks. Claims 26-29 and 32-40 are pending examination. Reconsideration is respectfully requested.

The declaration is being submitted unexecuted. An executed copy of the declaration will be filed with a supplemental response.

Rejections Under §103

Claims 26-30, 32-35 and 38-40 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Curiel et al. (U.S. 6,824,771) in view of Xu et al. (Human Gene Therapy, 1997; 8:177-185). Applicants respectfully disagree with the rejection.

According to the Examiner, Curiel et al. teaches a conditionally replicative recombinant adenovirus which has a functional E1B-19k and is E1B-55k-deleted or is Ea1A-deleted/modified and comprises a therapeutic gene operatively linked to a promoter. The Examiner recognizes that Curiel et al. does not teach that p53 is one of the therapeutic proteins. Rather, Curiel et al. uses thymidine kinase as an exemplary therapeutic gene.

Xu et al. is cited by the Examiner in an attempt to make up for the deficiencies with Curiel et al. The Examiner contends that it would have been obvious to substitute the particular anti-cancer protein, p53 from Xu et al., in the adenovirus of Curiel et al.

For the following reasons, Applicants disagree with the Examiner's line of reasoning:

In order to support a rationale that the combination of elements described in Xu et al. and Curiel et al. is obvious, such combination of elements must yield predictable results. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739-40 (2007). In addition, "predictable results" refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739-40 (2007). DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314 (Fed. Cir. 2009). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Applicants have provided a detailed explanation in their previous responses as to why the claimed combination would not have been predicted by a skilled person, nor would a skilled person have had a reasonable expectation of success. See, e.g., Response to Office Action, November 8, 2010, at pages 10-12.

The Examiner has found Applicants' arguments of record unpersuasive. In response, Applicants submit herewith a signed declaration by Dr. Frank McCormick, which supports

Applicants arguments that the combination of elements described in Xu et al. and Curiel et al. leads to unpredictable results. Dr. McCormick submits that the unexpected discovery that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy is highly novel and not predictable from previous research publications, including Xu et al., Curiel et al., and Lin et al. See McCormick Declaration, at, e.g., points 3 and 8.

As submitted in Applicants' previous response, it was expected from the prior art that restoration of functional p53 in a replication competent adenovirus would suppress viral replication. See Response to Office Action, November 8, 2010, at page 10. This result was suggested by Hermiston and Kuhn (Cancer Gene Therapy, 2002; 9:1022-1035) and is based on the observation that p53 is actively degraded during viral replication, and adenoviruses that fail to degrade p53 are defective for replication in normal primary human cells (O'Shea et al, Cancer Cell, 2004). This view was re-enforced recently by O'Shea and coworkers (Soria et al, Nature 2010 – a copy is attached to the McCormick Declaration as Exhibit B) who showed that adenoviral E4 proteins contribute to inactivation of p53 during infection, in addition to the well-known effect of E1B 55K on p53 degradation.

Therefore, restoration of functional p53 would be expected to suppress virus replication in a replication competent adenovirus rather than enhancing it. See McCormick Declaration, at point 5.

Furthermore, as submitted in Applicants' previous response, it was not expected that p53 expressed in a replication competent adenovirus would remain functional. Response to Office Action, November 8, 2010, at page 11. Adenoviruses shut down host protein synthesis and synthesis of viral genes expressed from certain early promoters. It was therefore unexpected that p53 could remain functional (documented in van Beusechem et al., Cancer Research 2002; 62:6165-6171) and promote expression of downstream genes. The recent work of Soria et al. (*supra*) underscores the fact that adenoviruses encode multiple mechanisms to eradicate and inactivate p53 during infection.

Therefore, the activity demonstrated by the instant invention was therefore unexpected for several distinct reasons. See McCormick Declaration, at point 6.

Although the idea that direct, forced, expression of p53 in a p53-negative tumor cell promotes growth arrest, or cell death, has been well established for many years, this effect is clearly distinct from the novel role of p53 in promoting virus replication, as discovered in the instant application. The importance of the instant invention is based on the presumption that clinical efficacy depends on robust virus replication and infection of multiple tumor cells, rather than direct killing of a single transduced cell by a non-replicating viral vector. See McCormick Declaration, at point 7.

The Examiner has also recognized this distinction in the roles of p53 when stating that "the state of the art indicates that p53 dependent apoptosis is prevented through the action of the

E1B proteins". See Office Action, July 31, 2006, at page 7. However, figure 6 of the present application demonstrates that conditionally replicating adenovirus expressing both p53 and E1B-55 kDa effectively kills human cancer cells. In contrast to the teachings of the prior art, the effects of the present application are due to a novel role of p53 in promoting virus replication. See McCormick Declaration, at point 7.

For at least the foregoing reasons, it is submitted that the combination of elements described in Xu et al. and Curiel et al. would not have been expected to work for its intended purpose. The effect of the combination as recited in the claims could not be predicted and was not obvious. Indeed, the art taught away from the present invention as the combination was thought to be ineffective. See McCormick Declaration, at points 3-8.

In view of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al. is respectfully requested.

Claims 36-37 stand rejected under §103 as allegedly being unpatentable over Curiel et al., in view of Xu et al., as applied to claims 26 and 35 above, and further in view of Lin et al. (Cancer Res. Oct 15, 2000. 60:5895-5901). Applicants traverse the rejection.

Lin et al. is relied on for teaching a mutant form of human p53. However, Lin et al. is silent regarding the effect of restoration of functional p53 in a replication competent adenovirus. Lin et al. is also silent regarding the novel role of p53 in promoting virus replication, as

discovered in the instant application. The disclosure of Lin et al. thus fails to remedy the deficiency that the combination of elements described in the cited references would not have been expected to work for its intended purpose.

The effect of the combination as recited in claims 36-37 could not be predicted and was not obvious. Indeed, the art taught away from the present invention as the combination was thought to be ineffective. See McCormick Declaration, at points 3-8.

In view of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al., and further in view of Lin et al. is respectfully requested.

It is now believed that the application is in condition for allowance. If the Examiner believes a telephone discussion would be beneficial to resolve any outstanding issue, he is invited to contact the undersigned without hesitation.

Respectfully submitted,

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